



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C08F 220/18, 220/30, G02B 1/04	A1	(11) International Publication Number: WO 00/61646 (43) International Publication Date: 19 October 2000 (19.10.00)
(21) International Application Number: PCT/US00/08288 (22) International Filing Date: 29 March 2000 (29.03.00) (30) Priority Data: 60/128,751 12 April 1999 (12.04.99) US 09/358,757 22 July 1999 (22.07.99) US (71) Applicant: SURGIDEV CORPORATION [US/US]; 5743 Thornwood Drive, Goleta, CA 93117 (US). (72) Inventor: MENTAK, Khalid; 5743 Thornwood Drive, Goleta, CA 93117 (US). (74) Agent: MEIER, Linda, Blair, Michael Best & Friedrich LLP, P.O. Box 1806, Madison, WI 53701-1806 (US).		(81) Designated States: CA, JP, RU, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: WATER PLASTICIZED HIGH REFRACTIVE INDEX POLYMER FOR OPHTHALMIC APPLICATIONS (57) Abstract A high refractive index, foldable polymer suitable for use in ophthalmic devices, such as intraocular lenses, is provided. The polymer may be produced from a polymerization reaction of first, second and third monomeric components and a crosslinking agent. The first monomeric component includes an aryl acrylate or an aryl methacrylate. The second monomeric component, which is not an acrylate, includes a monomer having an aromatic ring with a substituent having at least one site of ethylenic unsaturation. The third monomeric component includes a high water content hydrogel-forming monomer. The resulting high refractive index copolymer is durable enough to be cut and polished when dry, and becomes soft and foldable when hydrated.		

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**WATER PLASTICIZED HIGH REFRACTIVE INDEX
POLYMER FOR OPHTHALMIC APPLICATIONS**

This invention relates to copolymer materials which are useful as ophthalmic devices, such as contact lenses, intraocular lenses (IOLs), keratoprotheses, and corneal
10 rings or inlays, and a process for making and using such copolymer materials. In particular, this invention relates to intraocular foldable lenses formed from acrylic copolymer materials.

With recent advances in small-incision cataract surgery, increased emphasis has been placed on developing soft, foldable materials suitable for use in artificial ophthalmic
15 lenses. In general, these materials fall into one of three categories: hydrogels, silicones, and generally, others.

The refractive power of a lens is a function of its shape and the refractive index of the material of which it is made. A lens made from a material having a higher refractive index can be thinner and provide the same refractive power as a lens made from a material
20 having a relatively lower refractive index. Thinner lenses are easier to insert and cause less trauma during surgery.

Hydrogel materials are hard or rigid when dry, and absorb a large amount of water (for example, up to 20-70% by weight) when hydrated, which lowers the refractive index of the material. These materials tend to be brittle when dry, and have poor mechanical
25 properties for ophthalmic applications. In a hydrated state, hydrogel materials become soft and pliable. Known hydrated hydrogels have a relatively low refractive index, for example, less than 1.48. In addition to adversely affecting the refractive index, the absorbed water also significantly increases the diameter and thickness of the IOLs, for example, by as much as about 15 percent.

30 Silicone materials have a slightly higher refractive index (for example, 1.51), but tend to unfold too rapidly after being placed in the eye in a folded configuration. The biocompatibility of silicone materials may also be a concern.

U.S. Patent Nos. 5,290,892 (Namdaran et al.), 5,331,073 (Weinschenk, III et al.), and 5,693,095 (Freeman et al.) discuss forming foldable lenses out of a polymer material
35 derived from an ethoxyaryl (meth)acrylate with a crosslinker or with a second acrylate monomer and crosslinker. Since the polymer material is soft/foldable, those patents discuss mold forming the polymer material to individually form the lens. Likewise, U.S. Patent No. 5,433,746 to Namdaran et al. discloses forming flexible intraocular lenses by

- 5 c) a third monomeric component which is a high water content hydrogel-forming monomer. Preferably, the copolymer further includes a crosslinking agent.

Another aspect of the invention is an ophthalmic device made from the copolymer of the invention.

10 The invention also provides a process for making ophthalmic devices such as intraocular lenses from the polymer(s) disclosed. The process generally involves forming a rigid polymer work piece from the copolymer of the invention, forming an ophthalmic device from the work piece, and hydrating the ophthalmic device to a sufficiently soft and flexible state so that, if desired, the device can be folded.

15 A further aspect of the invention is a method of implanting an ophthalmic device within an eye. The method involves providing a hydratable ophthalmic device which is rigid at room temperature when dry, and foldable at room temperature when hydrated. The ophthalmic device is hydrated and a syringe is provided which contains the hydrated ophthalmic device. The ophthalmic device is then injected into the eye.

20 DESCRIPTION OF THE INVENTION

The polymer material of the present invention comprises polymer units derived from the polymerization of first, second, and third monomeric components. These components may include aryl (meth)acrylate monomer, an aromatic monomer, and a high water content hydrogel-forming monomer, respectively. Preferably a crosslinking agent is included. Each of the components is described below in more detail.

25 The composition may optionally include other monomeric components, an initiator, or an ultraviolet (UV) absorbing material. The proportions of the monomers should preferably be chosen to produce a substantially rigid polymer having a glass transition temperature of at least about normal room temperature. Each of the three different monomeric components is preferably present in the copolymer in an amount of at least about 10 weight percent, more preferably, at least about 20 weight percent. This invention contemplates preparation of random and block copolymers of the monomeric components discussed herein. Unless otherwise stated, all weight percents are based on the total weight of the composition prior to polymerization.

35 In a highly preferred embodiment, the composition comprises a hydratable copolymer which includes:

- a) at least 20 weight percent of a first monomeric component such as ethylene glycol phenyl ether acrylate or polyethylene glycol phenyl ether acrylate;

5 methyphenylethyl methacrylate, 2-3-methylphenylethyl methacrylate, 2-4-methylphenylethyl methacrylate, 2-(4-propylphenyl)ethyl methacrylate, 2-(4-(1-methylethyl)phenyl)ethyl methacrylate, 2-(4-methoxyphenyl)ethylmethacrylate, 2-(4-cyclohexylphenyl)ethyl methacrylate, 2-(2-chlorophenyl)ethyl methacrylate, 2-(3-chlorophenyl)ethyl methacrylate, 2-(4-chlorophenyl)ethyl methacrylate, 2-(4-bromophenyl)ethyl methacrylate, 2-(3-phenylphenyl)ethyl methacrylate, 2-(4-phenylphenyl)ethyl methacrylate), 2-(4-benzylphenyl)ethyl methacrylate, and the like, including the corresponding methacrylates and acrylates, and including mixtures thereof. Other aryl acrylate monomers and aryl methacrylate monomers are likely to occur to one skilled in this art in light of the present disclosure. EGPEA and polyEGPEA are preferred.

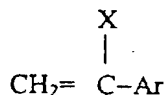
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The first monomeric component should be added to the composition in an amount sufficient to provide high refractive index, a moderate water uptake, and enhanced backbone rigidity. Preferably, the first monomeric component comprises at least about 10 weight percent of the composition; more preferably, at least about 20 weight percent; most preferably, at least about 30 weight percent. The first monomeric component should be added in an amount to avoid an undesirably low glass transition temperature in the resulting copolymer. Preferably, the first monomeric component comprises less than about 60 weight percent of the composition; more preferably, less than about 50 weight percent; most preferably, less than about 45 weight percent.

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The second monomeric component includes a monomer having an aromatic ring with a substituent having at least one site of ethylenic unsaturation. Preferably, this second monomeric component is not an acrylate. Such monomers correspond to the general formula (II):

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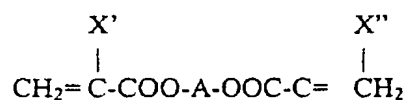
35 where X is -H or -CH₃, and Ar is a substituted or unsubstituted aromatic ring.

Representative second monomeric components include, for example, substituted and unsubstituted styrene compounds. These compounds may be substituted with hydrogen, halogen (e.g. Br, Cl, F), lower alkyl groups (e.g. methyl, ethyl, propyl, butyl,

5 preferably, less than about 50 weight percent; most preferably, less than about 40 weight percent.

The copolymer may also include a crosslinking agent. The copolymerizable crosslinking agent(s) useful in forming the copolymeric material of the invention include
 10 any terminally ethylenically unsaturated compound having more than one unsaturated group. Preferably, the crosslinking agent includes a diacrylate or a dimethacrylate. The crosslinking agent may also include compounds having at least two (meth)acrylate and/or vinyl groups. Particularly preferred crosslinking agents include diacrylate compounds represented by the following formula (III):

15



20 wherein X' and X'' separately and independently represent a hydrogen atom or a methyl group; and A represents a substituted or unsubstituted divalent hydrocarbyl group. In a preferred form of formula (III), A represents a substituted or unsubstituted divalent aliphatic radical, and preferably a 1-6 carbon alkylene.

Representative crosslinking agents include, for example: diacrylate compounds
 25 including ethylene glycol dimethacrylate (EGDM), diethylene glycol dimethacrylate, polyethylene glycol dimethacrylate, alkyl methacrylate, 1-3-propanedioldimethacrylate allymethacrylate, 1,6-hexanediol dimethacrylate, 1,3-butanediol dimethacrylate, 1,4-butanediol dimethacrylate as well as, divinyl compounds including divinyl hydrocarbons and divinyl benzene, and the like. Ethylene glycol dimethacrylate is preferred.

30 The crosslinking agent should be added in an amount sufficient to permit the hydrated copolymer to return to its original shape after being folded. Preferably, the crosslinking agent comprises at least about 1 weight percent of the composition; more preferably, at least about 3 weight percent. Conversely, the crosslinking agent should be added in an amount low enough avoid making the copolymer too rigid or brittle.
 35 Preferably, the crosslinking agent comprises less than about 10 weight percent of the composition; more preferably, less than about 5 weight percent.

One skilled in the art will appreciate that additives such as ultraviolet (UV) blocking agents, colorants, etc. optionally may be added to the polymer of this invention

5 The resulting ophthalmic device is then hydrated. This may be achieved by soaking the ophthalmic device in an aqueous solution (such as water or saline), preferably at an elevated temperature (for example, between 20-100°C), for sufficient time to inculcate the device with water (e.g. for a time period of from several minutes to several hours or longer).

10 An ophthalmic or other device fabricated from a polymer of the present invention does not significantly expand or change shape when hydrated. In other words, there is no statistically significant difference between the diameter and thickness of the dry device and that of the hydrated device. Thus, for IOLs, the rigid intraocular lens and the foldable hydrated intraocular lens have essentially the same dimensions.

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COPOLYMER PROPERTIES

The copolymers of the invention have a unique combination of desirable characteristics, for example, high refractive index, good mechanical properties, high glass transition temperature, optical clarity, hydratability, and foldability once hydrated.

20 A particularly advantageous combination of properties includes having a copolymer which is foldable at room temperature despite having a glass transition temperature above room temperature, and which also has a refractive index (RI) greater than about 1.50. Because the refractive index of the hydrated copolymer tends to be greater than 1.50 (and the preferred copolymers have a refractive index greater than about
25 1.55), the copolymers are especially attractive for ophthalmic applications such as intraocular lenses. The refractive power of a lens is a function of its shape and the refractive index of the material of which it is made. A lens made from a material having a higher refractive index can be thinner and provide the same refractive power as a lens made from a material having a relatively lower refractive index. Thinner lenses are easier
30 to insert and cause less trauma during surgery. Thus, in general, the higher the refractive index, the better the material with other factors remaining the same. RIs of at least 1.558 have been attained.

The mechanical properties of the copolymer, such as the glass transition temperature, permit it to be cut and polished (that is, machined) at room temperature
35 (rather than molded, or shaped at cryogenic temperatures). The copolymer is rigid at normal room temperature when dry, and flexible at normal room temperature when hydrated. In other words, the dry copolymer is rigid or solid enough at room temperature to be workable by conventional cutting or lathing; and the hydrated copolymer is flexible

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SURGICAL METHOD

Employing the copolymer of the invention, cataract surgery may be carried out through an incision of 1.5 millimeters or less. After applying topical anesthesia to the eye, an IOL made of the new copolymer material may be injected into the eye. No sutures are necessary in this process.

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A method of implanting an ophthalmic device within an eye may be carried out by providing a hydratable ophthalmic device which is rigid at room temperature when dry, and foldable at room temperature when hydrated. The ophthalmic device is hydrated and a syringe is provided which contains the hydrated ophthalmic device. The ophthalmic device, which is preferably an intraocular lens made of the copolymer of the invention, is then injected into the eye. Desirably, the ophthalmic device is injected into the eye through an incision less than about 1.5 millimeters in length.

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The lens may be inserted using a device, for example, like that described in U.S. Patent No. 4,715,373 to Mazzocco. The shape or fixation system used to position the IOL in the eye is not critical to this invention. The copolymers may be used in a foldable lens having a variety of fixation systems. See, for example, U.S. Patent No. 5,776,191 to Mazzocco for a discussion regarding fixation systems for IOL structures.

20

EXAMPLES

Example 1

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Various copolymers are prepared by mixing the following ingredients under reduced pressure: a first, second and third monomeric component, a crosslinker and a polymerizable UV blocking agent. Vinyl benzotriazole at a total concentration of 0.3% by weight is utilized as the UV blocking agent. To initiate polymerization a free radical initiator 2-2'-azobisisobutyronitrile (AIBN) is employed at concentration of 0.2% by weight. The monomer solution is mixed in a glass flask using a magnetic stir bar for 30 minutes. The solution is then filtered through a 0.2 micron (μ) filter and injected into a sheet mold comprising two glass plates held together with spring clips and separated by a plastic gasket. The mold is then placed in a water bath for 10 hours at 60°C, then removed and post cured at 95°C in oven for 12 hours. A clear, hard polymer sheet is obtained.

30

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Intraocular lenses of various diopters (5, 10, 20, and 34) are cut from the rigid plastic sheet using conventional machining techniques as used to manufacture polymethylmethacrylate (PMMA) IOLs.

5

TABLE I

Formulation	1st Monomer	2nd Monomer	3rd Monomer	Cross-linker	EWC (Weight %)	Machinability	Foldability	RI (hydrated)	Expansion %
1	40% EGPEA	26% styrene	30% HEMA	4% EGDM	4	Good	Fair	1.551	1.5
2	35% EGPEA	26% styrene	35% HEEMA	4% EGDM	3.8	Good	Fair	1.551	1.5
3	40% poly EGPEA	20% chloro-styrene	36% HEMA	4% EGDM	3.5	Fair	Poor	1.552	1.3
4	43% EGPEA	26% styrene	27% meth-acrylic acid	4% EGDM	4.1	Good	Fair	1.551	1.8
5	25% poly EGPEA	11% styrene	60% HEMA	4% EGDM	12.1	Fair	Fair	1.523	5.8
6	40% poly EGPEA	26% styrene	30% HEMA	4% EGDM	4.0	Good	Good	1.551	0.1
7	45% poly EGPEA	31% styrene	20% HEMA	4% EGDM	1.3	Good	Poor	1.556	0.1
8	50% poly EGPEA	36% styrene	10% HEMA	4% EGDM	1.1	Good	Poor	1.554	0.1
9	25% poly EGPEA	11% styrene	60% HEEMA	4% EGDM	16.5	Poor	Fair	1.509	7.2
10	40% poly EGPEA	26% styrene	30% HEEMA	4% EGDM	9.2	Poor	Fair	1.514	6.5
11	45% poly EGPEA	31% styrene	20% HEEMA	4% EGDM	4.6	Poor	Fair	1.533	2.3
12	50% poly EGPEA	36% styrene	10% HEEMA	4% EGDM	5.3	Poor	Fair	1.541	3.6
13	40% poly EGPEA	28% styrene	30% HEMA	2% EGDM	5.1	Fair	Good	1.551	0.3
14	34% poly EGPEA	31% styrene	32% HEMA	3% EGDM	5.0	Fair	Fair	1.553	0.4
15	41% poly EGPEA	26% styrene	31% HEMA	2% EGDM	4.5	Poor	Fair	1.552	3.1
16	41% poly EGPEA	27% styrene	31% HEMA	1% EGDM	4.8	Poor	Fair	1.549	4.6
17	20% poly EGPEA	40% styrene	40% HEMA	1% EGDM	3.2	Good	Poor	1.551	2.1
18	41% poly EGPEA	27% chloro-styrene	31% HEMA	1% EGDM	5.1	Fair	Fair	1.547	2.1
19	40% poly EGPEA	26% chloro-styrene	30% HEMA	4% EGDM	4.2	Fair	Fair	1.551	0.2

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- 5 material can be machined if environmental parameters can be controlled. for example, by decreasing the temperature. Poor machinability means the material tends to deform or break when lathe cut, but it is still machinable if environmental parameters are controlled. Not machinable means the material cannot be cut with a lathe and must be formed using methods such as molding. "Foldability" refers to the ability to bend the material as much
10 as about 180° without breaking once the material has been hydrated. Good foldability means the material can be easily folded using forceps when the material is cut into a disk about the size of a standard lens. Fair foldability means a hydrated disk of the material folds when applying little force. Poor foldability means the hydrated disk folds without breaking when a greater force is applied.

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Example 2

A hydration study was conducted to assess the change in dimension after complete hydration. Twenty samples of each formulation described in Example 1 were used. Samples consisted of disks 16.5 millimeters in diameter and 2.0 millimeters in thickness.

- 20 The results were averaged for each formulation.

Formulation	% Change in Diameter	% Change in Thickness
1	0.02 + 0.01	0.04 + 0.01
2	0.05 + 0.02	0.08 + 0.02
3	0.06 + 0.01	0.08 + 0.01
4	0.08 + 0.03	0.06 + 0.01

There were no significant dimensional changes after hydration.

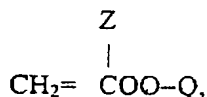
5 9. The copolymer of claim 1 wherein the copolymer further comprises a crosslinking agent.

10. The copolymer of claim 1 wherein the copolymer has a glass transition temperature greater than room temperature.

10

11. The copolymer of claim 1 wherein the copolymer is machinable at normal room temperature and has a refractive index greater than 1.50.

12. The copolymer of claim 1 wherein the first monomeric component corresponds to
15 the formula:



20 wherein:

Z is - H or -CH₃, and

Q is a substituent containing at least one aromatic ring.

13. The copolymer of claim 12 wherein Q is selected from the group consisting of:
25 ethylene glycol phenyl ether, poly(ethylene glycol phenyl ether acrylate), phenyl, 2-ethylphenoxy, 2-ethylphenoxy, hexylphenoxy, hexylphenoxy, benzyl, 2-phenylethyl, 4-methylphenyl, 4-methylbenzyl, 2-2-methylphenylethyl, 2-3-methylphenylethyl methacrylate, 2-4-methylphenylethyl, 2-(4-propylphenyl)ethyl, 2-(4-(1-methylethyl)phenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(4-cyclohexylphenyl)ethyl, 2-(2-
30 chlorophenyl)ethyl, 2-(3-chlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(4-bromophenyl)ethyl, 2-(3-phenylphenyl)ethyl, 2-(4-phenylphenyl)ethyl, and 2-(4-benzylphenyl)ethyl.

14. The copolymer of claim 1 wherein the first monomeric component is selected from
35 the group consisting of ethylene glycol phenyl ether acrylate, poly(ethylene glycol phenyl ether acrylate), phenyl methacrylate, 2-ethylphenoxy methacrylate, 2-ethylphenoxy acrylate, hexylphenoxy methacrylate, hexylphenoxy acrylate, benzyl methacrylate, 2-phenylethyl methacrylate, 4-methylphenyl methacrylate, 4-methylbenzyl methacrylate, 2-2-methylphenylethyl methacrylate, 2-3-methylphenylethyl methacrylate, 2-4-

5 methoxyethoxyethyl methacrylate, methoxydiethoxyethyl methacrylate, ethylene glycol dimethacrylate, n-vinyl-2-pyrrolidone, methacrylic acid, vinyl acetate, and mixtures thereof.

23. The copolymer of claim 1 wherein the third monomeric component is selected
10 from the group consisting of hydroxyethyl methacrylate, hydroxy ethoxyethyl methacrylate, and methacrylic acid.

24. The copolymer of claim 1 wherein the copolymer includes at least 10 weight
15 percent of the third monomeric component.

25. The copolymer of claim 9 wherein the crosslinking agent comprises a diacrylate or a dimethacrylate.

26. A hydratable copolymer comprising:

20 a) at least 20 weight percent of a first monomeric component selected from the group consisting of ethylene glycol phenyl ether acrylate, and polyethylene glycol phenyl ether acrylate;

b) at least 10 weight percent of a second monomeric component selected from the group consisting of substituted styrene and unsubstituted styrene;

25 c) at least 10 weight percent of a third monomeric component selected from the group consisting of hydroxy ethyl methacrylate, hydroxyethoxy ethyl methacrylate, and methacrylic acid; and

d) less than 10 weight percent of a crosslinking agent selected from the group consisting of a diacrylate and a dimethacrylate,

30 wherein the copolymer has a refractive index greater than 1.50, and is foldable at normal room temperature when hydrated.

27. The copolymer of claim 26 wherein the crosslinking agent comprises ethylene
35 glycol dimethacrylate.

28. The copolymer of claim 26 wherein the first monomeric component comprises polyethylene glycol phenyl ether acrylate, the second monomeric component comprises

5 32. The ophthalmic device of claim 31 wherein the ophthalmic device is an intraocular lens.

33. A method of manufacturing an intraocular lens, the method comprising:

- 10 a) providing a rigid, hydratable copolymer comprising
a first monomeric component which comprises an aryl acrylate or an aryl methacrylate;
a second monomeric component which comprises a monomer having an aromatic ring
with a substituent having at least one site of ethylenic unsaturation, wherein the second
monomeric component is other than an acrylate; and
15 a third monomeric component which comprises a high water content hydrogel-forming
monomer,
wherein the copolymer has a glass transition temperature greater than normal room
temperature;
b) forming a rigid intraocular lens having the desired dimensions from the rigid
copolymer; and
20 c) hydrating the copolymer to form a foldable, hydrated intraocular lens,

wherein the hydrated intraocular lens has an equilibrium water concentration less than 10
weight percent, and a refractive index greater than 1.55.

25 34. The method of claim 33 wherein the rigid intraocular lens and the foldable
hydrated intraocular lens differ in volume by less than 10%.

35. The method of claim 33 wherein the intraocular lens is a 20 diopter lens and has a
central thickness less than 0.4 millimeter.

30

36. The method of claim 33 wherein the copolymer is hydrated by:
placing the copolymer in an aqueous solution;

gradually increasing the temperature of the aqueous solution to 40°C;

holding the temperature of the aqueous solution at 40°C for at least 10 minutes;

35 gradually increasing the temperature of the aqueous solution to 60°C;

holding the temperature of the aqueous solution at 60°C for at least one hour; and

gradually decreasing the temperature of the aqueous solution to room temperature.

- 5 the second monomeric component comprises a monomer having an aromatic ring with a substituent having at least one site of ethylenic unsaturation, the second monomeric component being other than an acrylate; and
the third monomeric component comprises a high water content hydrogel-forming monomer; and
- 10 b) subjecting the reaction mixture to polymerization conditions to form the copolymer.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: lonal Application No

PCT/US 00/08288

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